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TITLE: TREATMENT OF ADULT SEVERE TRAUMATIC BRAIN INJURY
USING AUTOLOGOUS BONE MARROW MONONUCLEAR CELLS

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14. ABSTRACT Traumatic brain injury (TBI) contributes to 50% of all trauma deaths. The mortality rate for adults following severe TBI (Glasgow Coma Scale < 9) is estimated to be 33%. There is currently no therapy to reverse the primary injury associated with TBI. There has been a growing body of literature supporting the use of various progenitor cell types to treat acute neurological injuries such as TBI. Our primary hypothesis is that bone marrow mononuclear cell (BMMNC) autologous transplantation after TBI is safe. Our secondary hypothesis is that functional outcomes measures will improve after BMMNC infusion, (3) BMMNC infusion will reduce BBB permeability and (4) BMMNC is neuroprotective and preserves grey and white matter volumes after TBI. This is a dose-escalation study consisting of 4 cohorts including a control group. The 1st five subjects in the treatment group will receive the lowest dose target of 6×10^6 mononuclear cells/kilogram body weight. The next five subjects will receive 9×10^6 mononuclear cells/kilogram body weight, and the last five subjects in the treatment group will receive 12×10^6 mononuclear cells/kilogram body weight. The 10 subjects in the control group will not undergo the bone marrow harvest procedure; though they will be followed and treated the same as the other study participants and complete all follow-up procedures. All subjects (including those in the control group), will be followed for safety, have plasma & CSF (if available) collected for neuroinflammatory markers. The 1 & 6 mo. follow-up visits include physical and neurological exams, neuropsych. & functional outcomes tests, blood sample for routine labs and neuroinflammatory markers, & a DTMRI. A final outcome assessment will be conducted by telephone 1 to 2.5yr. post TBI. Per protocol, the medical monitor has reviewed all subject records and no serious adverse events related to the BMMNC infusion have been reported. The DSMB met on 10 January 2014 & reviewed safety data on the 17 subjects enrolled in the study at that time. No subject safety issues were identified and the DSMB recommended the study continue as is with no protocol modifications. Our most recent clinical monitor visit was 11 March 2014. As of 31 DEC 2014, 25 subjects have enrolled in the study and 24 have completed the 1 mo. follow-up visit. One control group subject was lost to follow-up after discharge. Eighteen Subjects have completed the 6 mo. end of study visit and the remainder have appointments scheduled. The results presented in this report represent preliminary data analysis. Final data analysis will occur after all the final study visits are completed.					
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TREATMENT OF ADULT SEVERE TRAUMATIC BRAIN INJURY USING AUTOLOGOUS BONE MARROW MONONUCLEAR CELLS

Annual Progress Report: 01 JUN 2014 to 31 DEC 2014

Introduction

Traumatic brain injury (TBI) contributes to 50% of all trauma deaths. The mortality rate for adults following severe TBI (Glasgow Coma Scale < 9) is estimated to be 33%. There are currently no effective treatments to prevent secondary brain injury after TBI, which manifests clinically as increased blood brain barrier (BBB) permeability and cerebral edema. Both have been directly linked to increased intracranial pressure (ICP) and early morbidity and mortality after TBI. Neurological damage after severe TBI does not entirely occur immediately at the moment of impact (primary injury), but evolves afterwards. A great deal of the secondary brain injury associated with TBI is caused by the effects of cerebral edema, leading to an increase in ICP and a subsequent decrease in cerebral perfusion. If poorly controlled, brain damage and increase mortality may result.

Extensive literature supporting the use of various progenitor cell types to treat acute neurological injuries has emerged in recent years. Neural stem cells (adult and embryonic), mesenchymal stromal cells (MSC), and multipotent adult progenitor cells (MAPC), and bone marrow mononuclear cells (BMMNC, from which MSC and MAPCs are derived) have all shown efficacy in pre-clinical models of TBI/stroke through various mechanisms; however, few believe that true neural replacement and integration are the putative mechanisms involved in observed efficacy. More likely is that the progenitor cell populations are modifying the regional response to injury (inflammatory/reparative vs. regenerative), resulting in improved functional outcomes. We have completed a pediatric Phase I clinical trial using the same entry criteria described below without any mortality or significant related infusion toxicity. The results of this study, the only trial to date with this design, were presented at the *Congress of Neurological Surgeons* meeting in October 2009. The completed study confirms the logistical feasibility and safety of the proposed approach.

Our primary hypothesis is that bone marrow mononuclear cell (BMMNC) autologous transplantation after TBI is safe (harvest and infusion related toxicity) after TBI. Our secondary hypothesis is that functional outcomes measures will improve after BMMNC infusion, (3) BMMNC infusion will reduce BBB permeability and (4) BMMNC is neuroprotective and preserves grey matter and white matter volumes after TBI (through Diffusion Tensor Magnetic Resonance Imaging or DTMRI).

Safety will be determined by monitoring cerebral and systemic hemodynamics during harvest and transplant, neurologic events (seizure, change in Glasgow Coma Score [GCS], cerebrovascular accident [CVA], etc.), infectious morbidity, and secondary organ injury. Intracranial pressure will be compared to pro and anti-neuroinflammatory markers, cytokines, and chemokines from plasma and cerebrospinal fluid (CSF, if available) collected over the first 5 days post-injury, and at 1 and 6 months post-injury. Late outcomes will be determined using a battery of neurocognitive tests.

Progress Report:

Enrollment and Follow-up Phase:

Patients, ages 18 to 55 years old, admitted to Memorial Hermann Hospital Trauma Center with Glasgow Coma Scores (GCS) of 5 to 8 are screened. Those patients meeting inclusion/exclusion criteria (or their Legal Authorized Representative [LAR]) are offered consent to participate by the investigator. This is a dose-escalation study consisting of 4 cohorts including a control group. The 10 subjects in the control group will not undergo the bone marrow harvest procedure; though they will be followed and treated the same as the other study participants and complete all follow-up procedures.

The 1st five subjects in the treatment group will receive the lowest dose target of 6×10^6 mononuclear cells/kilogram body weight. The next five subjects will receive 9×10^6 mononuclear cells/kilogram body weight, and the last five subjects in the treatment group will receive 12×10^6 mononuclear cells/kilogram body weight. All subjects will be followed for safety, have plasma and CSF (if available) collected for neuroinflammatory markers, and will return at 30-days and 6 months post-injury for neuropsychiatric and functional outcomes testing, DTMRI, and neuroinflammatory markers. A final outcome assessment will be conducted by telephone 1 to 2.5yr. post TBI.

As of 31 DEC 2014, 25 subjects have enrolled in the study. All subjects had in-patient plasma and CSF (when available) collected for pro and anti-neuroinflammatory markers, cytokines, and chemokines. One control group subject was a no-show for the 1 and 6 month visits, and is lost to follow-up. Twenty-four subjects have completed the 1 month study visit and 18 have completed the 6 month end of study visit. The remaining subjects will complete the 6 month end of study visit in MAR/APR of 2015. Per protocol, all subject records have been reviewed by the medical monitor and no serious adverse events related to the BMMNC infusion have been reported. The DSMB met on 10 January 2014 and reviewed safety data on the 17 subjects enrolled at that time. No subject safety issues were identified and the DSMB recommended the study continue as is with no protocol modifications. Our most recent clinical monitor visit was 21 JUL 2014.

Table 1: Cumulative Screening

	Screened	Enrolled	Refused	Eligible but Enrolled in Competing Study	Reason #1 for Exclusion	Reason #2 for Exclusion	Reason #3 for Exclusion
MAR 2012	12	1	0	1	GCS <5 or >8	> Grade 3 Injuries	Hx of prior brain injury
APR 2012	8	2	0	0	GCS <5 or >8	> Grade 3 Injuries	Hemodynamic Instability
MAY 2012	10	0	0	0	GCS <5 or >8	> Grade 3 Injuries	Hemodynamic Instability
JUN 2012	14	1	1	0	GCS <5 or >8	> Grade 3 Injuries	Hemodynamic Instability
JUL 2012	18	0	0	0	GCS <5 or >8	+ UDS	Hemodynamic Instability
AUG 2012	21	1	0	0	GCS <5 or >8	Hemodynamic Instability	HIV +
SEP 2012	17	0	1	2	GCS <5 or >8	Hemodynamic Instability	ICP > 40
OCT 2012	15	1	1	0	GCS <5 or >8	Hx of prior brain injury	Pulmonary Contusions
NOV 2012	17	1	0	0	GCS <5 or >8	pulmonary contusions	Pelvic Fractures
DEC 2012	12	0	0	1	GCS <5 or >8	ICP > 40	Hx of prior brain injury
JAN 2013	20	0	0	0	GCS <5 or >8	Hemodynamic Instability	Poor F/U
FEB 2013	12	2	0	0	GCS <5 or >8	Psychiatric Disorder	Poor F/U
MAR 2013	3	1	0	0	GCS <5 or >8	> Grade 3 Injuries	Penetrating Brain Injury
APR 2013	4	1	0	0	GCS <5 or >8	> Grade 3 Injuries	Hemodynamic Instability
MAY 2013	25	1	1	0	GCS <5 or >8	Hemodynamic Instability	> Grade I injuries
JUN 2013	18	0	0	0	GCS <5 or >8	> Grade 3 Injuries	Hemodynamic Instability
JUL 2013	14	2	0	0	GCS <5 or >8	> Grade 3 Injuries	Non-survivable Injury
AUG 2013	7	1	0	0	GCS <5 or >8	Unable to Obtain Consent	Penetrating Brain Injury
SEP 2013	9	1	0	1	GCS <5 or >8	Prolonged Hypoxia	Non-Survivable Injury

	Screened	Enrolled	Refused	Eligible but Enrolled in Competing Study	Reason #1 for Exclusion	Reason #2 for Exclusion	Reason #3 for Exclusion
NOV 2013	13	1	1	0	GCS <5 or >8	Non-Survivable Injury	> Grade 3 Injuries
DEC 2013	6	0	0	0	GCS <5 or >8	Prolonged Hypoxia	Pelvic Fractures
JAN 2014	12	0	0	0	GCS <5 or >8	Unable to Obtain Consent	Non-Survivable Injury
FEB 2014	6	0	0	0	GCS <5 or >8	Unable to Obtain Consent	Non-Survivable Injury
MAR 2014	12	1	0	0	GCS <5 or >8	Penetrating Brain Injury	Non-Survivable Injury
APR 2014	2	2	0	0	GCS <5 or >8	Unable to Obtain Consent	ICP > 40
AUG 2014	5	1	0	0	GCS <5 or >8	Penetrating Brain Injury	Non-Survivable Injury
SEP 2014	9	3	1	0	GCS <5 or >8	Unable to Obtain Consent	Psych. Disorder with Chem. Depend.
OCT 2014	1	1	0	0	GCS <5 or >8	Hemodynamic Instability	> Grade 3 Injuries
Totals	322	25	6	5			

Screening procedures ceased in April after reaching the study enrollment limit. Screening resumed in August after DoD and UT IRB approval to enroll additional controls, and was concluded in October after enrollment of the last control group subject.

Table 2: Cumulative Enrollment

Subject #	Enrollment Date	Age (years)	Gender	Race	Status
1	3/28/2012	18	M	Asian	All Visits Completed.
2	4/11/2012	19	M	African-American	No show for return visits. Considered lost to follow-up.
3	4/12/2012	51	M	White	All Visits Completed.
4	6/17/2012	52	F	White	All Visits Completed.
5	8/16/2012	41	M	White	All Visits Completed.
6	10/18/2012	33	M	African-American	All Visits Completed.
7	11/27/2012	20	M	White	All Visits Completed.
8	2/8/2013	17	F	White	All Visits Completed.
9	2/28/2013	37	M	White	All Visits Completed.
10	3/17/2013	19	M	White	All Visits Completed.
11	4/7/2013	44	M	White	All Visits Completed.
12	5/25/2013	22	M	White	All Visits Completed.
13	7/14/2013	28	F	White	All Visits Completed.
14	7/25/2013	33	M	White	All Visits Completed.
15	8/10/2013	28	M	White	All Visits Completed.
16	9/10/2013	23	M	White	All Visits Completed.
17	11/16/2013	34	F	White	All Visits Completed.
18	3/28/2014	43	F	White	Completed 1 month visit, 6 mo. visit scheduled.
19	4/6/2014	36	M	African-American	All Visits Completed.
20	4/7/2014	36	M	Hispanic	All Visits Completed.
21	8/30/2014	25	F	Hispanic	Completed 1 month visit, 6 mo. visit scheduled.
22	9/12/2014	31	M	Hispanic	Completed 1 month visit, 6 mo. visit scheduled.
23	9/15/2014	18	M	White	Completed 1 month visit, 6 mo. visit scheduled.
24	9/21/2014	54	M	Hispanic	Completed 1 month visit, 6 mo. visit scheduled.
25	10/6/2014	34	F	White	Completed 1 month visit, 6 mo. visit scheduled.

Preliminary Analysis of Primary Safety Outcomes (Aim 1):

Safety: Safety data was collected for all 25 subjects during hospitalization. Adverse events were reported for all cohort groups, as expected for patients with severe TBI. No adverse events were associated with, or temporally related to the stem cell infusion. Analysis of the infused cellular product is presented in Table 3 below.

Table 3:

Flow Cytometric Analysis of Infused Cellular Product

Marker	6 x 10 ⁶ TNC/Kg	9 x 10 ⁶ TNC/Kg	12 x 10 ⁶ TNC/Kg
	Mean% ± Standard Error (SE) n=5	Mean% ± Standard Error (SE) n=5	Mean% ± Standard Error (SE) n=5
Cell Viability	94.42 ± 1.44	96.92 ± 0.94	98.22 ± 0.48
Total CD34 ⁺	1.91 ± 0.35	2.12 ± 0.34	1.85 ± 0.18
Lin ^{neg} CD34 ⁺	1.51 ± 0.26	1.97 ± 0.31	1.61 ± 0.14
Lin ^{neg} CD34 ⁺ CD	0.20 ± 0.06	0.53 ± 0.40	1.30 ± 0.19
Lin ^{neg} CD34 ⁺ CD133 ⁺	1.31 ± 0.24	1.43 ± 0.47	0.31 ± 0.19
Lin ^{neg} CD34 ⁺ CD 133 ⁺	1.13 ± 0.26	1.14 ± 0.34	0.02 ± 0.01
T-cells	65.43 ± 4.59	72.70 ± 2.50	70.80 ± 3.02
B-cells	19.61 ± 4.24	13.34 ± 3.38	14.91 ± 2.46
NK-cells	10.84 ± 1.43	9.23 ± 1.38	7.17 ± 1.41
4 Part Differential			
Lymphocytes	29.97 ± 3.20	32.27 ± 3.10	38.42 ± 4.06
Monocytes	33.00 ± 2.91	22.53 ± 2.18	26.1 ± 4.26
Granulocytes	23.09 ± 3.37	26.20 ± 2.05	18.34 ± 2.85
Blasts	5.32 ± 0.61	5.76 ± 0.87	5.13 ± 0.62

Preliminary Analysis of Functional Outcomes (Aim 2):

Global Outcomes: As noted above, we have enrolled 25/25 patients in this trial, however, the follow-up is still ongoing. We have noted some parallels in the pediatric and adult data in terms of GOS-E improvement with cell therapy with time. Tables 4 and 5 below outline our results, and importantly, there is a trend to improvement with treatment over time.

Table 4:

	CONTROL	LOW	MID	HIGH
No change	3	1	1	2
+1 category	1	1	2	
+2		2		
+3 or more		1	2	
Chi square for GOS change:				
Control vs Combined Low/Middle Dose: p = .095				

Table 5:

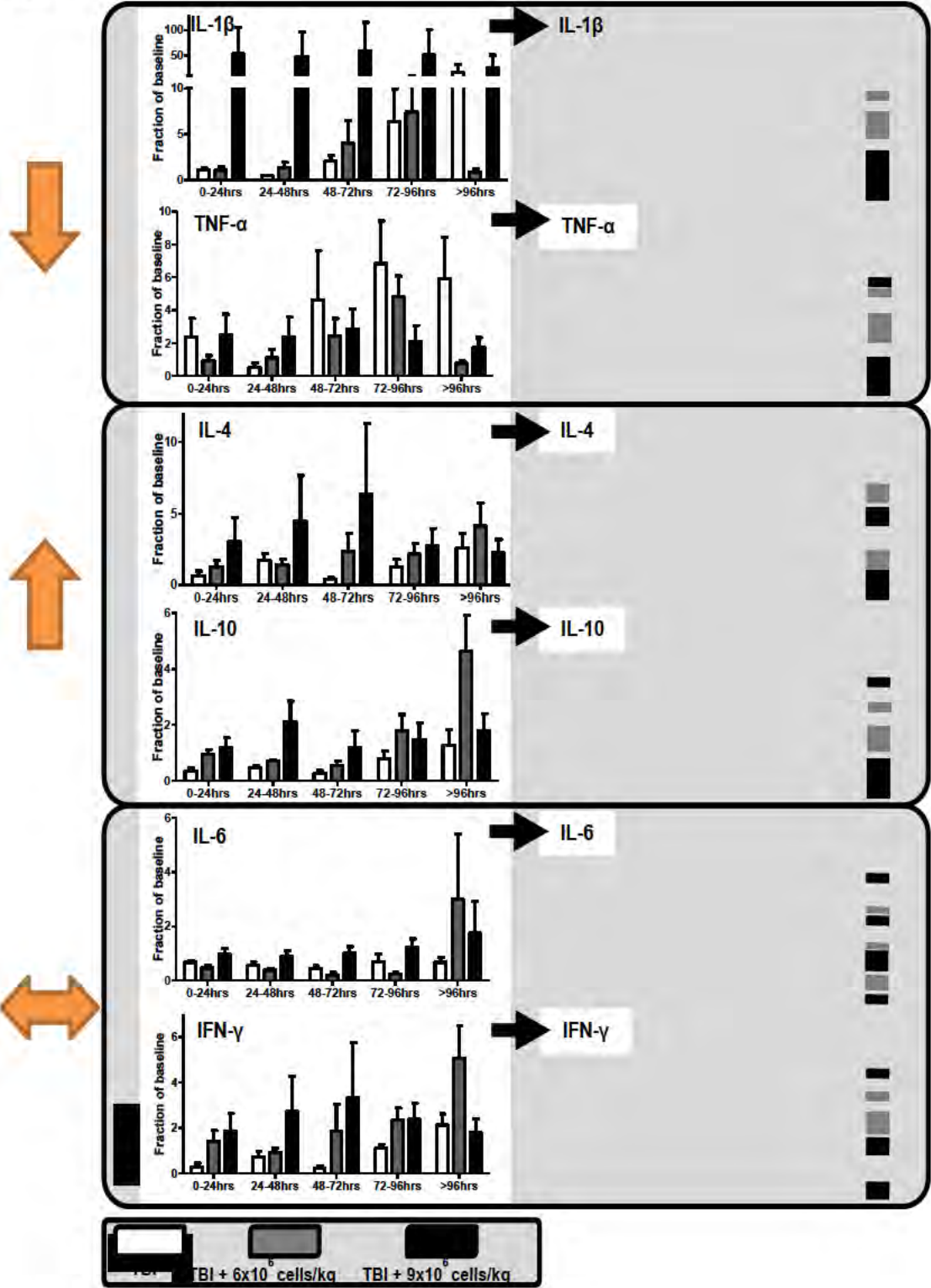
	Control		Low Dose		Middle Dose		Low + Mid Dose		High Dose	
GOS-E Category (n)	1m	6m	1m	6m	1m	6m	1m	6m		
Vegetative			1				1	0		
Severe Disability										
Lower	3	2	4	2	5	1	9	3	5	2
Upper	1	1				2	0	2		
Moderate Disability										
Lower				2			0	2		
Upper		1		1		1	0	2		
Good Recovery										
Lower						1	0	1		
Upper										

Preliminary Analysis of Neuroinflammatory Markers (Aim 3):

Modulation of pro/anti-Inflammatory Cytokines: Interval plasma samples from 24–96 hours post TBI were obtained from three groups (TBI alone (n=3), TBI+6 million cells/kg (n=4), TBI+9 million cells/kg (n=5)). All samples have not been analyzed, as this is ongoing at time of this submission. The cell therapy groups were treated intravenously within 48 hours of injury. A multiplex magnetic bead-based assay was used to quantify select pro- (IL-1 β , IL-6, IFN- γ , TNF- α) and anti- (IL-4, IL-10) inflammatory cytokines. Standard analysis normalized each cytokine to baseline levels per patient. Then hierarchical clustering was used on the raw data to generate dendrogram heat maps using Pearson correlated row distance measures and pairwise average-linkage clustering (GenePattern, Broad Institute). Each cytokine dendrogram heat map was examined to determine if rows (patients) stratified according to treatment group. Hierarchical clustering and dendrogram heat map generation identified IL-1 β , IL-4, IL-10 and TNF- α as cytokines where the dendrogram pattern correlated with the assigned treatment groups. The dendrogram clustering also demonstrated a treatment dose dependent reduction for the pro-inflammatory cytokines IL-1 β and TNF- α , and a dose dependent increase for the anti-inflammatory cytokine IL-4 from 24–96 hours. IL-10 exhibited a dose related increase.

The data in figure 1 below supports the concept that autologous BMMNC infusion after severe TBI in adults down-regulates pro-inflammatory cytokines and up-regulates anti-inflammatory cytokines. The up-regulation of IL-4 and IL-10 are associated with polarization of the endogenous microglia to a M2/reparative phenotype. There was no demonstrated effect on IL-6 or interferon gamma.

Figure 1:



Preliminary Analysis of Structural Tissue Preservation (Aim 4):

Correlation of FA of Corpus Callosum Region with Outcomes: Differences Between Treatment Groups

Effect sizes (Cohen's d) were calculated to examine whether area, FA, or MD from the whole CC at 6 months after TBI differed in the untreated patients compared with those in the low and medium dose groups. The intervention had a small effect on CC area ($d = 0.354$) and moderate effects on FA, $d = 0.710$ and MD, $d = 0.662$. All effects were in the expected direction, consistent with a small effect of preservation of size of the CC and moderate effects for preservation of FA and MD in the treated group.

Regarding functional outcomes, a small to moderate positive effect of the intervention on functional outcome was noted for the GOS-E, $d = 0.422$, and the Mayo-Portland Adaptability Inventory composite score, $d = 0.395$, but not for the Disability Rating Scale, $d = -0.017$, for the treated group relative to the untreated group. Table 6 provides means, SDs, and effect sizes for whole CC and selected functional and neuropsychological outcomes obtained 6 months post-injury.

Table 6:	Dosage Group				
Outcomes	Untreated (n = 4)		Low/Medium (n = 10)		Effect Size **
	Mean	SD	Mean	SD	Cohen's d
Whole CC					
Area	582.38	49.62	609.90	98.12	0.354
Fractional Anisotropy	0.54	0.05	0.58	0.06	0.710
Mean Diffusivity	0.98	0.06	0.94	0.05	0.662
Functional and Neuropsychological					
GOS-Extended	4.00	1.41	4.60	1.43	0.422
Disability Rating Scale	4.75	2.63	4.80	3.12	- 0.017
Mayo-Portland Composite	46.25	7.27	42.20	12.53	0.395
Processing Speed Index	82.00	21.66	78.40	17.21	-0.184
Grooved Pegboard Dominant Hand z score	-2.07	2.49	-1.47	2.77	0.227
**Note: positive d = better outcome in treated versus no dose group					

Relation of Fractional Anisotropy from Callosal Regions with Functional and Neuropsychological Outcomes

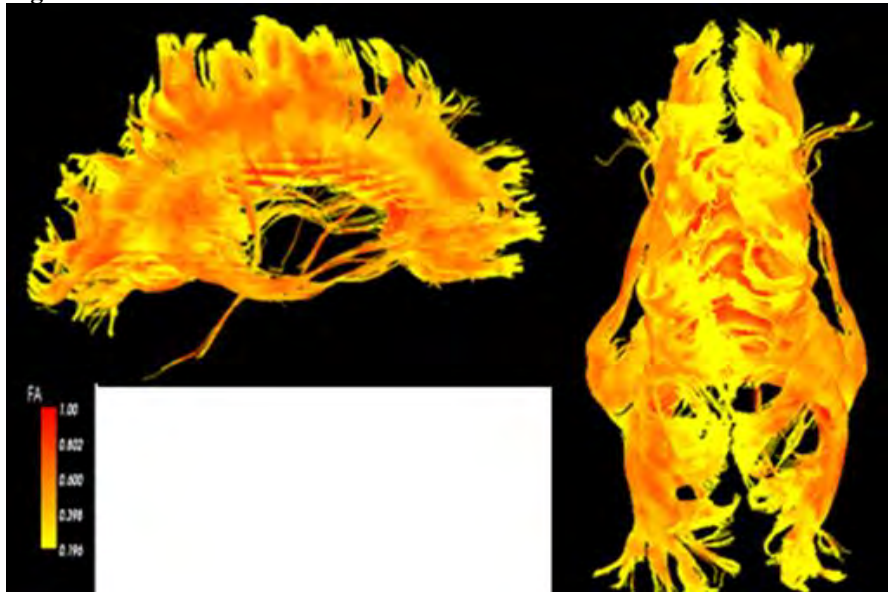
The corpus callosum is a brain structure with properties that make it a good candidate for use as a surrogate marker for clinical outcomes. With the improvement in MR imaging, the impact of diffuse axonal injury on clinical outcomes after TBI has been a focus of research in blunt TBI without mass lesions. Also, CC volumes are a good reflection of grey matter viability as the absence of CC atrophy indicates the absence of Wallerian degeneration from cortical neuronal cell death. Table 7 below demonstrates that for the total sample, area of the CC was not significantly related to any outcomes. FA of the splenium (CC5) and the whole CC were significantly related to all major functional outcomes, confirming that more favorable outcomes were seen in patients with greater tissue integrity. FA from specific CC regions correlated with age-standardized neuropsychological outcomes. Tasks

with a major motor component (Trail Making A, Coding, Grooved Pegboard), were significantly related to CC2 and/or CC3, which carry fibers from motor, premotor, and supplementary motor regions. Symbol search, a core component of processing speed, was related to CC2-5, reflecting the adverse impact of generalized white matter injury on tasks requiring speed and efficiency. Some outcomes were more strongly related to specific CC regions (e.g., Rey verbal memory test) while others were more strongly related to integrity of the whole CC (e.g., Trail Making B). Our ability to integrate sensitive metrics from both of our main outcome domains, neuroimaging and behavior, will enhance our ability to detect intervention effects.

Table 7: Correlation of Fractional Anisotropy of Corpus Callosum Region with Outcomes r (p)						
Outcomes	CC1	CC2	CC3	CC4	CC5	Whole CC
Functional						
GOS-E	0.269 (.353)	0.217 (.456)	0.313 (.277)	0.517 (.056)	0.767 (.001)	0.708 (.005)
Disability Rating Scale	-0.098 (.739)	-0.186 (.526)	-0.234 (.421)	-0.329 (.250)	-0.554 (.040)	-0.513 (.061)
Mayo-Portland Adaptability Index- Composite	-0.358 (.209)	-0.185 (.528)	-0.173 (.555)	-0.281 (.330)	-0.543 (.045)	-0.547 (.043)
Neuropsychological						
Trailmaking Test A	-0.168 (.566)	0.545 (.044)	0.607 (.021)	0.258 (.374)	0.528 (.052)	0.513 (.060)
Trailmaking Test B	0.426 (.146)	0.428 (.144)	0.466 (.108)	0.479 (.098)	0.481 (.096)	0.664 (.013)
WAIS Symbol Search	0.067 (.820)	0.576 (.031)	.652 (.012)	0.591 (.026)	0.626 (.012)	.737 (.003)
WAIS Coding	0.265 (.383)	0.805 (.001)	0.763 (.003)	0.465 (.110)	0.478 (.098)	0.711 (.007)
Grooved Pegboard-Dominant Hand	-0.198 (.537)	0.561 (.058)	0.647 (.023)	0.430 (.163)	0.687 (.014)	0.641 (.025)
Rey Auditory Verbal Learning Test Trial 6 recall	0.134 (.647)	0.622 (.018)	0.562 (.037)	0.271 (.348)	0.238 (.412)	0.454 (.103)

Microstructural Outcomes: MD is used for both WM and GM. Although clarification of the microstructural correlates of these metrics is ongoing, FA is believed to index the integrity and degree of fiber tract organization. MD assesses ease of water movement; in well-organized WM and GM, barriers to diffusion include both neuronal and glial cellular membranes. Increased diffusion has been associated with cellular breakdown, ultimately leading to atrophy. The images in figure 2 below are corpus callosal WM fiber tracts with FA noted in color (more orange is greater FA/myelination).

Figure 2:



This fiber tract map of the corpus callosum is from a normal brain. Each fiber tract can be quantified individually by the imaging analysis. Note for reference the fiber density and the degree of FA (greater orange color denotes greater FA or myelination).

The graphs in figures 3 and 4 demonstrate GM/WM volumetric changes and CC fiber tract numbers that occurred in the interval between 1 and 6 months post-injury. **These preliminary data demonstrate both, total GM/WM volumetric preservation in a dose dependent manner, but also a more pronounced effect on CC fiber tract count. This is critical preliminary data as it supports the primary outcome measure proposed in the trial.**

Figure 3:

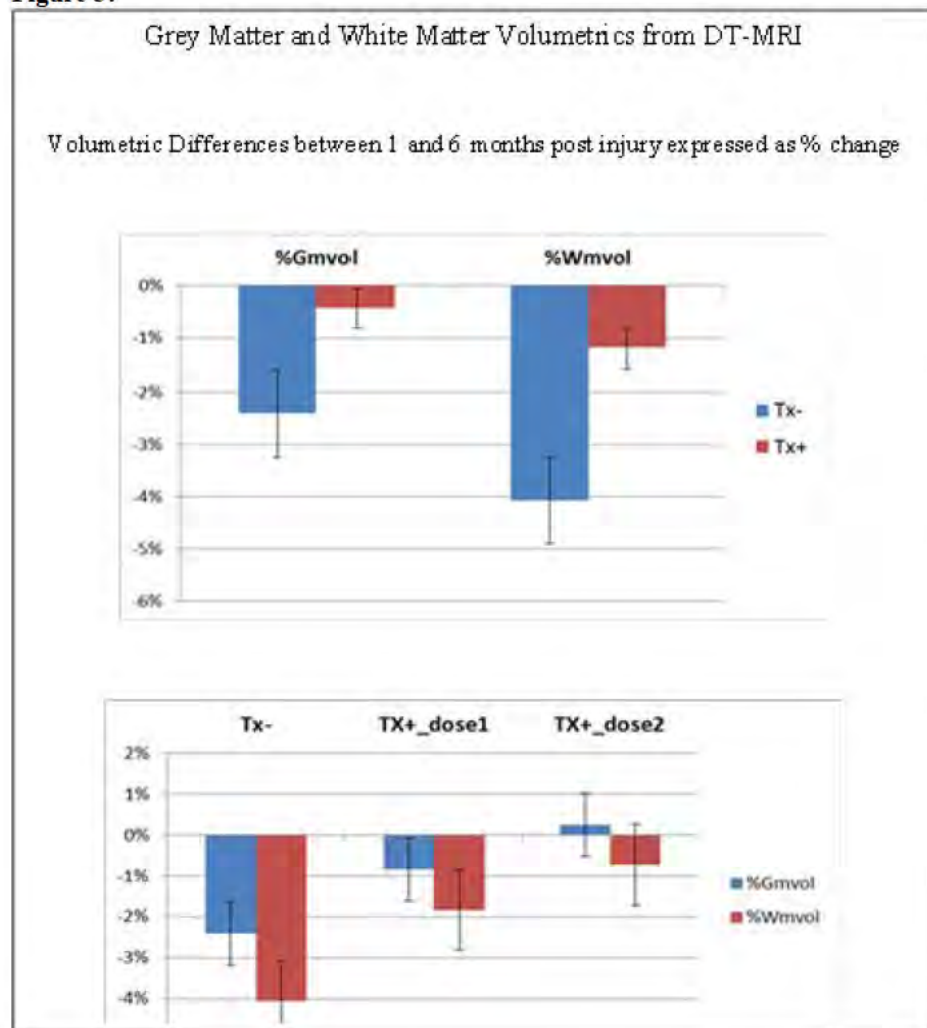
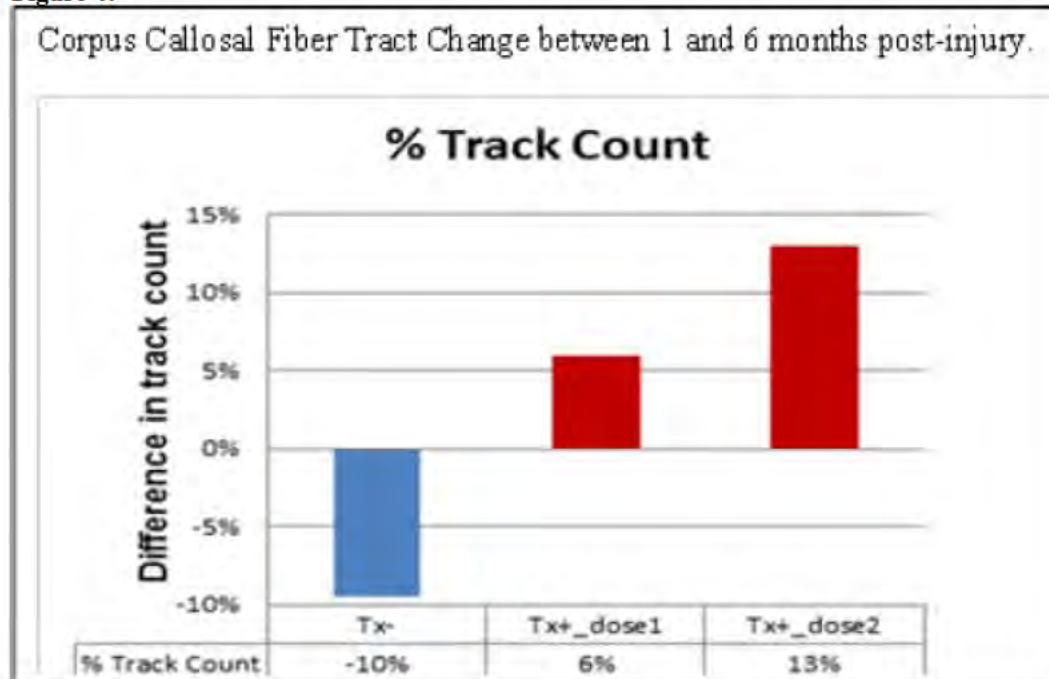


Figure 4:



These data are fiber tract counts from the CC, derived from all of the individual images as in Figures 5-6 which are examples of treated and untreated patients. Each yellow/orange line is an individual fiber tract. There is a dose-dependent increase in fiber tract count with a greater effect size than with whole brain volumes. Fiber tract count has been shown to correlate positively with outcome after TBI. (Wilde, 2012). Callosal fiber tract loss is due to the discrete vulnerability of the CC to rotational shear forces. Tx-: Control patients; Tx_dose 1: 6×10^6 cells/kg; Tx_2: 9×10^6 cells/kg.

Figure 5:

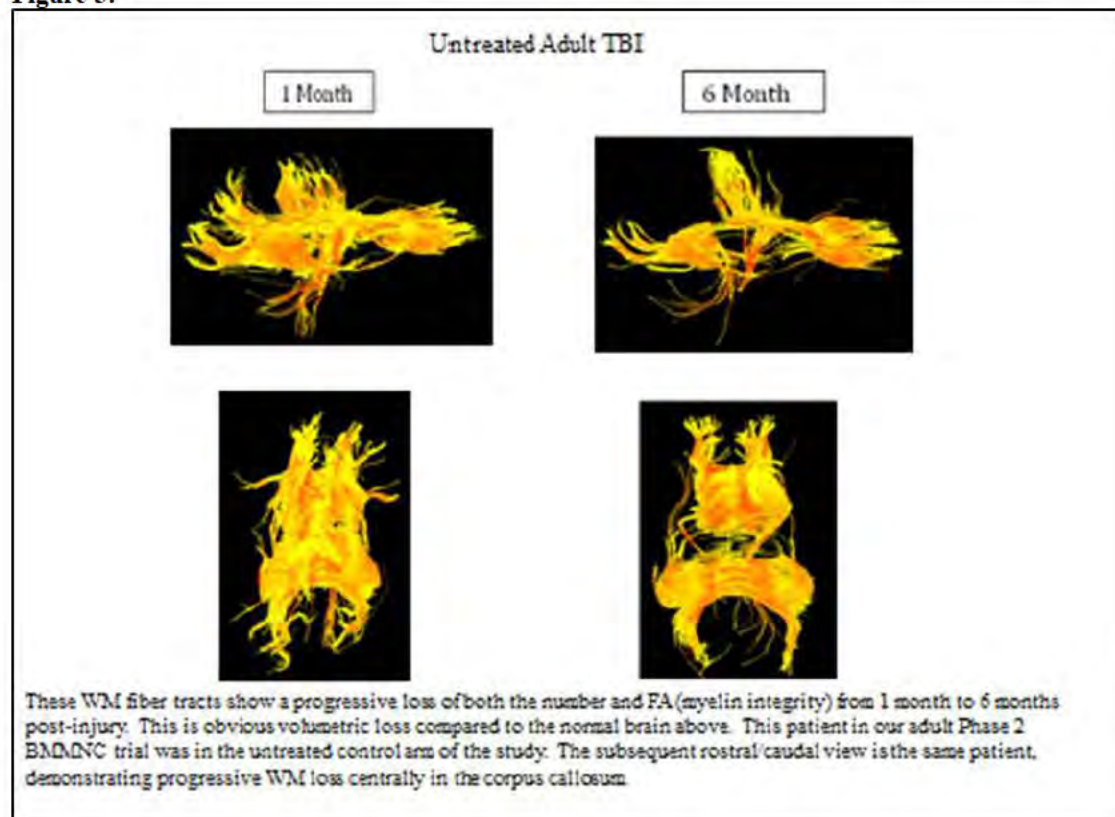
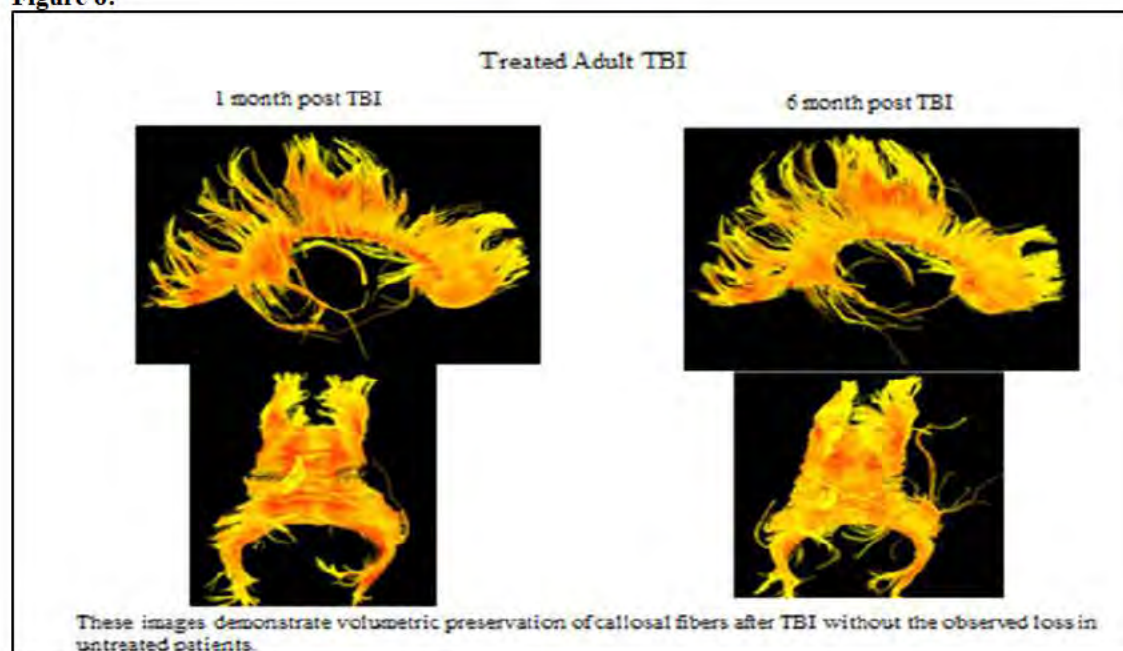


Figure 6:



Key Research Accomplishments:

FY11 Goals- Regulatory Approval of Protocol

- ☑ FDA IND Approved APR 2011, IRB Approved OCT 2011, and HRPO Approved DEC 2011.

FY12 Goals - Study Initiation & Enrollment

- ☑ Enrollment of 1st Cohort Group (5 Controls) Started MAR 2012, Completed AUG 2012.
- ☑ Enrollment of 2nd Cohort (6×10^6 BMMNC/kg) Started OCT 2012.

FY13 Goals - Safety Monitoring & Dose Escalation

- ☑ Enrollment of 2nd cohort (6×10^6 BMMNC/kg) completed MAR 2013.
- ☑ Enrollment of 3rd cohort (9×10^6 BMMNC/kg) started APR 2013.
- ☑ DSMB review of safety data JUN 2013 with recommendation to continue study.
- ☑ Enrollment of 3rd cohort (9×10^6 BMMNC/kg) completed AUG 2013.
- ☑ Enrollment of 4th cohort (12×10^6 BMMNC/kg) started SEP 2013.

FY14 Goals – Completion of Enrollment & Data Analysis

- ☑ DSMB review of safety data JAN 2014 with recommendation to continue study.
- ☑ Enrollment of 4th cohort (12×10^6 BMMNC/kg) completed APR 2014.
- ☑ UTHHealth IRB approval to enroll additional controls and conduct a final outcome assessment telephone calls for all subjects received AUG 2014.
- ☑ Enrollment of 5 additional controls completed OCT 2014 with follow-up visits pending.
- ☑ Data analysis is underway.

Reportable Outcomes/Conclusions: This annual report contains results from preliminary data analysis. Final data analysis will begin when all subject visits have been completed.

References: None